

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/B2004/001440

International filing date (day/month/year)
08.04.2004

Priority date (day/month/year)
09.04.2003

International Patent Classification (IPC) or both national classification and IPC
C07K14/195, A61K39/02, C12N15/31, C07K16/12

Applicant
CHIRON SRL

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/001440

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☒ contained in the international application as filed.
 - ☒ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
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Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

**WRITTEN OPINION OF THE
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International application No.
PCT/IB2004/001440

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 2-6(all partially), 7,28

because:

- ☒ the said international application, or the said claims Nos. 28 with respect to IA relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 2-6(all partially), 7
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/001440

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. Invention 1: claims 1(complete),2-6(partially),8-28(all partially)

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	12
	No: Claims	1-6,8-11,13-28
Inventive step (IS)	Yes: Claims	
	No: Claims	1-6,8-28
Industrial applicability (IA)	Yes: Claims	1-27
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III.

1. No complete search report has been established for the mutations claimed in claim 2 to 6. Thus, the opinion will only refer in general to mutations of SEQ.ID.NO.:1.
2. Claim 28 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(I) PCT).

Re Item IV.

The separate inventions/groups of inventions are:

Invention 1: claims 1-6(all complete),8-28(all partially)

The protein consisting of SEQ.ID.NO.:1, antibodies against this protein, DNA sequences and medical uses thereof.

Invention 2-12: claim 7(complete),8-28(all partially)

The 11 different point mutations of SEQ.ID.NO.: 1 as listed in table 1 and uses thereof.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The present application discloses an ADP-ribosylating toxin of *Listeria monocytogenes* characterised by SEQ.ID.NO.: 1 (claim 1). Moreover, 11 different point mutations thereof are claimed in present claim 7 being listed in table 1 of the present application. The common special technical feature linking the wild-type sequence and the different point mutations thereof is the protein of SEQ.ID.NO.: 1. A search in the different sequence databases revealed that SEQ.ID.NO.: 1 was already known from the prior art.

In the light of the prior art, the problems underlying the present application can be seen as the provision of further sequences coding for an ADP-ribosylating toxin of *Listeria monocytogenes*. The solution can be summarised as the provision of SEQ.ID.NO.: 1 of claims 1 and the 11 different point mutations thereof as claimed in present claim 7. However, the protein of SEQ.ID.NO.: 1 was already known from the prior art (see protein having accession number Q8YAAQ1 of the Uniprot database and sequence number 921 of WO-A-0177335). This finding takes away the common special technical feature linking the wild-type sequence with the different point mutations claimed. Moreover, no other technical

feature can be distinguished which in the light of the prior art could be regarded as a special common technical feature linking the twelve different proteins of claims 1 and 7 mentioned above. Thus, the ISA is of the opinion that there is no single inventive concept underlying the plurality of different inventions in the sense of Rule 13.2 PCT. Consequently, there is a lack of unity and the different inventions not belonging to a common inventive concept are formulated as different groups of inventions pursuant to Art. 17(3)(a) PCT. In consequence, only the first invention comprising claims 1-6 (all complete), 8-28 (all partially) will be dealt with in the following opinion.

Re Item V.

The following documents are referred to in this communication:

D1 : DATABASE UNIPROT 1 March 2002 (2002-03-01), GALSER ET AL:
retrieved from EBI, Database accession no. Q8YAQ1

D2 : DATABASE GSP 18 October 2001 (2001-10-18), BUCHRIESER ET AL:
retrieved from EBI, Database accession no. ABB48216

D3: WO-A-0177335

1. Claim 1 refers to a protein being characterised by SEQ.ID.NO.: 1.

This sequence is known from D1 (see abstract and corresponding links to its function as an A/B toxin), D2 (see accession number) and D3 (see sequence 921 and its function as a toxin (page 89, line 23 and 24). Thus, the subject-matter of claim 1 is not considered to be novel and does not comply with the requirements of Art. 33(2) PCT.

D3 moreover, discloses not only the sequence of claim 1 but also pharmaceutical compositions, fragments, mutations, diagnostic kits, vaccines and antibodies against said sequences (see abstract, page 1, lines 1 to 16, page 3, line 33 to page 4, line 28, page 15, line 28 to page 16, line 13, page 30, line 7 to page 31, line 13, page 37, line 18 to 26, page 38, line 28 to page 39, line 9). Thus, D3 is considered to be detrimental to the novelty of the subject-matter of claims 1 to 6, 8 to 11, 13 to 28.

In summary, the subject-matter of claims 1 to 6, 8 to 11 and 13 to 28 is not considered to be novel and does not comply with the requirements of Art. 33(2) PCT.

2. Moreover, the subject-matter of claims 1 to 6 and 8 to 28 is not considered to be

inventive for the following reasons:

The sequence of claim 1 was already known from the prior art (see D1 to D3, mentioned above). Moreover, its putative function as A/B toxin was also known (see D1 and D3). Consequently, the skilled person being beware of the existence of said toxin had a high motivation to use it since Listeriosis is one of the most problematic diseases for food industry. Consequently, presence of an inventive step cannot be acknowledged (Art. 33(3) PCT).

3. For the assessment of the present Claim 28 on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.